1. NAME OF THE MEDICINAL PRODUCTS

Frisium® 10mg

Clobazam

[sanofi logo]

Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg clobazam. Contains lactose (see section 4.4).
For the full list of excipients, see section 6.1.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Acute and chronic anxiety states, which may produce the following symptoms in particular: Anxiety, tension, restlessness, excitement, irritability, sleep disturbances from emotional causes, psychovegetative and psychosomatic disorders (for example, in the cardiovascular or gastro-intestinal area), and emotional instability.
In cases of psychovegetative and psychosomatic disorders, the doctor should investigate the possibility of an organic cause.
Before treatment of anxiety states associated with emotional instability, it must first be determined whether the patient suffers from a depressive disorder requiring adjuvant of different treatment.

- As adjunctive therapy in patients with epilepsy who are not adequately stabilized with their anticonvulsant mono-therapy.

4.2 Posology and method of administration

Dosage

Pharmaceutical presentation, dosage, and duration of treatment must be adjusted to the individual clinical response, the indication, and the severity of the condition. Due regard must be paid to the possibility of interference with alertness and reaction time. The fundamental principle is to keep the dose as low as possible.
When treatment with Frisium10 is to be discontinued after prolonged administration, the dosage should normally be tapered off over a period of time.

Treatment of anxiety states:
Adults and adolescents over 15 years of age: The initial dose is usually 20mg Frisium10 daily. If necessary, the daily dose may be increase to 30mg. Generally, it is recommended that a total daily dose of 30 mg is not exceeded.

Elderly: Increased responsiveness and higher susceptibility to adverse effects may be present in elderly patients and require low initial doses and gradual dose increments under careful observation. A total daily dose of 10-15mg is often enough.

Children from 3 to 15 years of age: Increased responsiveness and higher susceptibility to adverse effects may be present in children and require low initial doses and gradual dose increments under careful observation. A daily dose of 5-10 mg is frequently sufficient. Benzodiazepines must not be given to children without careful assessment of the need for their use.

Secondary dosage adjustment: After improvement of the symptoms, the dose may be reduced.

Timing of doses: If the dose is to be spread throughout the day, it is recommended that the larger portion be taken in the evening.

Duration of treatment: The duration of treatment must be as short as possible. The patient must be re-assessed after a period not exceeding 4 weeks and regularly thereafter in order to evaluate the need for continued treatment, especially where the patient is free of symptoms. Generally, the overall duration of treatment (i.e. including tapering-off process) must not exceed 8 to 12 weeks. In certain cases, extension beyond the maximum treatment period may be necessary; treatment must not be extended without a re-evaluation of the patient's status using special expertise. It is strongly recommended that prolonged periods of uninterrupted treatment be avoided, since they may lead to dependence.

Discontinuation of treatment*:* After improvement of the symptoms, the dose may be reduced. After prolonged treatment, Frisium10 should not be withdrawn suddenly. The dose should be reduced gradually under medical supervision, otherwise symptoms such as restlessness, anxiety, and insomnia may occur.

T*reatment of epilepsy in combination with one or more other antiepileptics:*
Adults and adolescents over 15 years of age: Small doses (5-15mg/day as the initial dose), gradually increasing to a maximum daily dose of about 80mg. Furthermore, constant doses (e.g. 20mg/day) and intermitted therapy (discontinuing Frisium10 and subsequently prescribing it again) have proven effective.

Children from 3 to 15 years of age: Treatment should normally be started with 5mg, and a maintenance dose of 0.3-1.0 mg/kg body weight daily is usually enough. Higher susceptibility to adverse effects may be present in children and require gradual dose increments under careful observation; Benzodiazepines must not be given to children without careful assessment of the need for their use.

Elderly: Higher susceptibility to adverse effects may be present in elderly patients and require low initial doses and gradual dose increments under careful observation.
Timing of doses: If the dose is spread throughout the day, it is recommended that the larger portion be taken in the evening. Doses of up to 30 mg clobazam can also be administered as a single evening dose.

Duration of treatment: The patient must be re-assessed after a period not exceeding 4 weeks and regularly thereafter in order to evaluate the need for continued treatment.

Discontinuation of treatment: At the end of treatment – also in cases where there has been a poor response to therapy – the dose should be gradually reduced, because otherwise and increased proneness to seizures as well as other withdrawal symptoms cannot be excluded.

Administration
The tablets should not be swallowed whole with some liquid. If the dose is to be distributed over the day, the larger portion should be taken in the evening. Doses of up to 30mg Frisium10 can also be administered as a single evening dose.
The duration of treatment is determined by the doctors. After a period not exceeding 4 weeks, the doctor should decide whether continuation of treatment is necessary. Prolonged spells of uninterrupted treatment should be avoided, since they may lead to dependence.

4.3 Contraindications

Frisium must not be used in any of the following circumstances:
- hypersensitivity to the active substance, other benzodiazepines or to any of the excipients listed in section 6.1.
- myasthenia gravis
- severe respiratory insufficiency
- sleep apnoea syndrome
- severe liver dysfunction
- acute intoxication with alcohol or other centrally acting substances
- history of dependence on alcohol, medicinal products or drugs
- lactation

4.4 Special warnings and precautions for use
In patients with schizophrenia or other psychoses, benzodiazepines are recommended only as an additional medicinal product, i.e. not as the primary form of treatment.
In patients with depression or anxiety linked to depression, Frisium may only be used in combination with an appropriate concomitant medicinal product.

Not all states of tension, agitation and anxiety require treatment with a medicinal product. They are often a manifestation of physical or mental illness and can be influenced by other measures or treatment of the underlying disease.

Frisium may only be taken if prescribed by a doctor and under constant medical supervision. It is irresponsible to pass medicinal products prescribed for personal use on to others.

Alcohol
It is recommended that patients abstain from drinking alcohol during treatment with Frisium (increased risk of sedation and other adverse effects) (see section 4.5).

Risks from concomitant use of opioids and benzodiazepines

Concomitant use of benzodiazepines, including clobazam, and opioids may result in sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of opioids and benzodiazepines for use in patients for whom alternative treatment options are inadequate. If a decision is made to prescribe clobazam concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation (see section 4.5).

Amnesia
Anterograde amnesia may occur even if benzodiazepines are used in the normal dose range, but especially at higher dose levels.

Dependence
As with other medicinal products containing benzodiazepines, administration should only be continued if absolutely essential and after careful evaluation of the therapeutic benefit against the risk of habituation and dependence.

All benzodiazepines can lead to physical and psychological dependence, the risk of which increases with the dose and duration of treatment. Even daily administration for a few weeks puts the patient at risk of developing dependence. This applies not only to the misuse of high doses but also to the therapeutic dose range. Patients with a known history of alcohol or medicinal product abuse have a higher risk of developing dependence.

Rebound phenomena/withdrawal symptoms
A rebound phenomenon or withdrawal syndrome can occur, especially if benzodiazepines are withdrawn suddenly. For this reason, the treatment should end with a gradual reduction in the dose.

The reappearance of symptoms that originally led to treatment with Frisium in an intensified form (e.g. states of anxiety, epileptic seizures) is characteristic of a rebound phenomenon. This may be accompanied by reactions such as mood swings, sleep disturbances and restlessness.

Once physical dependence has developed, sudden withdrawal of treatment with Frisium leads to withdrawal symptoms. Such symptoms include headache, muscle pain, sleep disturbances, increased dreaming, anxiety, states of tension, restlessness, confusion and agitation, tremor, sweating, symptomatic psychoses (e.g. withdrawal delirium) and epileptic seizures.

A withdrawal syndrome can also occur if treatment switches suddenly from a long-acting benzodiazepine (e.g. Frisium) to one with a short duration of action.

When Frisium is withdrawn after a prolonged period of use (more than a week), the dose should be reduced gradually. Consideration should be given to the possibility of temporary withdrawal phenomena. Abrupt withdrawal may provoke convulsions, especially if the medicinal product has been used as an anticonvulsant.

Development of tolerance
Patients should be expected to develop tolerance if Frisium is used as an anticonvulsant for several months.

Paradoxical reactions
During the use of benzodiazepines the occurrence of paradoxical reactions such as restlessness, irritability, aggression, delusion, anger, nightmares, hallucinations, psychotic disorders, agitation, sleep disturbances, suicidal ideation, increased muscle spasms and anxiety has been reported. Such reactions are to be especially expected in children and elderly people. If paradoxical reactions occur, treatment with clobazam should be discontinued.

Suicidal ideation/suicide attempts/suicide and depression
Several epidemiological studies indicate a greater incidence of suicidal ideations, suicide attempts and suicide in patients with or without depression who were treated with benzodiazepines or other hypnotics, including clobazam. However, no causal link has been proven (see section 4.8).

Therefore, patients should be monitored and a suitable treatment considered with respect to signs of suicidal thoughts and suicidal behaviour patterns. Patients (and their carers) should be advised to obtain medical help if signs of suicidal thoughts or suicidal behaviour occur.

Personality Disorders
Disinhibiting effects may be manifested in various ways. Suicide may be precipitated in patients who are depressed and aggressive behaviour towards self and others may be precipitated. Extreme caution should therefore be used in prescribing benzodiazepines in patients with personality disorders.

Serious skin reactions
Serious skin reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported with Frisium in both children and adults during post-marketing surveillance. A majority of the reported cases involved the concomitant use of other drugs, including antiepileptic drugs, that are associated with serious skin reactions.

SJS and TEN could be associated with a fatal outcome. Patients should be closely monitored for signs or symptoms of SJS/TEN, especially during the first 8 weeks of treatment. Clobazam should be immediately discontinued when SJS/TEN is suspected. In this case clobazam must no longer be used and alternative therapeutic options should be considered.

CYP2C19 poor metabolisers
In patients who are CYP2C19 poor metabolisers, levels of the active metabolite N-desmethylclobazam are expected to be increased as compared to extensive metabolisers.

Dosage adjustment of clobazam may be necessary (e.g. low starting dose with careful dose titration).

Concomitant use with cannabidiol
The concurrent use of clobazam with medicinal and non-medicinal products containing cannabidiol can increase levels of n-desmethylclobazam, which leads to an increased incidence of drowsiness and sedation. It may be necessary to adjust the dose of clobazam. Non-medicinal products containing cannabidiol must not be used in combination with clobazam since they contain unknown quantities of cannabidiol and differ in terms of quality (see sections 4.5 and 5.2).

High-risk patients
At the start of treatment, the treating doctor should monitor the individual response of the patient to the medicinal product in order to detect any relative overdoses as quickly as possible. This applies particularly to children, elderly patients and patients in poor general condition as well as to patients with organic brain changes, circulatory failure or respiratory failure. Patients should also be given specific instructions for everyday life, taking into account their specific situation (e.g. occupation).

Patients with renal and hepatic impairment
In patients with impairment of renal or hepatic function, responsiveness to Frisium (intensified and prolonged effect) and susceptibility to adverse effects might be increased and therefore dose reduction might be necessary. In long-term treatment renal and hepatic function must be checked regularly.

Elderly patients
In elderly patients there might be an increased sensitivity to adverse reactions such as drowsiness, dizziness and muscle weakness. Therefore, a dose reduction is recommended (see section 4.2 and 4.8).

Care should be taken in elderly patients especially when getting up at night due to risk of fall.

Children
Benzodiazepines must not be given to children without careful assessment of the need for their use (see section 4.2).

Respiratory depression
Clobazam can cause respiratory depression, especially if administered at high doses. Therefore, in patients with chronic or acute respiratory insufficiency, respiratory function

must be monitored and a dose reduction may be necessary. Clobazam is contraindicated in patients with severe respiratory insufficiency (see section 4.3).

Muscle weakness
Clobazam can cause muscle weakness. Therefore, in patients with pre-existing muscle weakness or spinal or cerebellar ataxia, Frisium should only be used with particular caution and if necessary with reduced dose. Clobazam is contraindicated in patients with myasthenia gravis (see section 4.3).

Long-term treatment
As a precaution, hepatic and renal function should be monitored during long-term treatment.

Frisium contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take Frisium.

4.5 Interaction with other medicinal products and other forms of interaction

Central nervous system depressant drugs/alcohol
If other medicinal products with a depressant effect on the central nervous system (e.g. neuroleptics, tranquillisers, antidepressants, hypnotics/sedatives, anaesthetics, beta blockers, opiate analgesics, sedative antihistamines, antiepileptics) are taken at the same time as high doses of Frisium in particular, each is likely to intensify the effect of the other. This applies particularly to concomitant alcohol consumption, which can alter or intensify the effects in an unpredictable way. Alcohol can increase the bioavailability of clobazam by 50%, thereby intensifying the effect of Frisium. For this reason, the patient should refrain from drinking alcohol during treatment with Frisium.

Opioids
The concomitant use of benzodiazepines, including clobazam, and opioids increases the risk of sedation, respiratory depression, coma, and death because of the additive CNS depressant effect. Limit dosage and duration of concomitant use of benzodiazepines and opioids (see section 4.4).

MAO inhibitors
If medicinal products that inhibit the monooxygenase system, such as cimetidine and erythromycin, are taken concurrently, the effect of Frisium may be intensified and prolonged.

Anticonvulsants
If anti-epileptics are being taken simultaneously for seizures, the adjustment phase of treatment must be conducted under medical supervision (EEG monitoring), as the medicinal product may interact with the anti-epileptic basic treatment. Concomitant administration of valproic acid and Frisium may result in a slight to moderate increase in the plasma concentration of valproic acid. Blood levels of phenytoin may rise if patients are treated with Frisium simultaneously. If possible, blood levels of valproic acid and phenytoin should be determined in such cases. Carbamazepine and phenytoin can lead to

an increase in the biotransformation of clobazam into the active metabolite N-desmethylclobazam. Stiripentol increases plasma levels of clobazam and its active metabolite N-desmethylclobazam through inhibition of CYP3A4 and CYP2C19. Monitoring of blood levels is recommended prior to initiation of stiripentol and then once a new steady-state concentration has been reached (i.e. after 2 weeks approximately).

Narcotic analgesics
If clobazam is used concomitantly with narcotic analgesics, possible euphoria may be enhanced; this may lead to increased psychological dependence.

Muscle relaxants/nitrous oxide
With concomitant use of muscle relaxants the muscle relaxing effect may be enhanced, especially in elderly patients and in case of higher dosage (risk of fall).
The effect of nitrous oxide may be enhanced.

CYP2C19 inhibitors
Strong and moderate inhibitors of CYP2C19 may result in increased exposure to N-desmethylclobazam (N-CLB), the active metabolite of clobazam. Dosage adjustment of clobazam may be necessary when co-administered with strong (e.g. fluconazole, fluvoxamine, ticlopidine) or moderate (e.g. omeprazole) CYP2C19 inhibitors (see section 5.2).

Cannabidiol
Concurrent administration of cannabidiol and clobazam produces bidirectional pharmacokinetic interactions. Data from a study of healthy volunteer subjects indicates that concurrent use with cannabidiol increases levels (3 to 4 times) of N-desmethylclobazam (an active metabolite of clobazam), probably as a result of CYP2C19 inhibition. Increased systemic levels of these active substances can lead to stronger pharmacological effects and an increase in undesirable drug effects. Concurrent use of cannabidiol and clobazam increases the incidence of drowsiness and sedation. A reduction of the clobazam dose should be considered if drowsiness or sedation occur when clobazam is used concomitantly with cannabidiol.

CYP2D6 substrates
Clobazam is a weak CYP2D6 inhibitor. Dose adjustment of drugs metabolized by CYP2D6 (e.g. dextromethorphan, pimozide, paroxetine, nebivolol) may be necessary.

4.6 Fertility, pregnancy and lactation
Pregnancy

There is only a limited amount of data from the use of clobazam in pregnant women. A large amount of data collected from cohort studies has not yielded evidence of severe fetal malformations with the use of benzodiazepines in the first trimester of pregnancy, although some specific case control studies revealed cases of cleft lip and cleft palate.

Clobazam is not recommended during pregnancy or in women of childbearing potential not using contraception.

Clobazam crosses the placenta. Animal studies have demonstrated reproductive toxicity (see section 5.3).

Women of childbearing potential should be informed about the benefits and risks of using clobazam during pregnancy and should be instructed to contact their doctor about discontinuing clobazam if they become pregnant or plan to become pregnant. If treatment with clobazam is continued, the lowest effective dose should be used.

Cases of reduced fetal movement and variability in fetal heart rate have been described with the use of benzodiazepines during the second and third trimesters of pregnancy.

If clobazam is administered during the later stages of pregnancy or during childbirth, effects may occur in the newborn, such as respiratory depression (including respiratory distress and apnoea), signs of sedation, hypothermia, hypotonia and feeding difficulties (floppy infant syndrome).

Additionally, the children of mothers who used benzodiazepines long-term in the later stages of pregnancy may develop a physical dependency, thus creating a risk of withdrawal symptoms after birth. Appropriate monitoring of the newborn in the postnatal period is recommended.

Breast-feeding
Frisium must not be taken during lactation because the active substance clobazam passes into breast milk. If treatment is absolutely essential, the infant should be weaned.

Fertility
No disturbance of fertility was observed in fertility studies in animals (see section 5.3). However, exposure in animals was less than the maximum recommended therapeutic dose.

4.7 Effects on ability to drive and use machines
Even if used as instructed, this medicinal product may affect reactions to such an extent that the ability to drive or use machines is impaired. This applies particularly in combination with alcohol.

Therefore, patients should refrain from driving, using machines or undertaking any other hazardous activities entirely, or at least for the first few days of treatment. The decision in each individual case is made by the treating doctor, taking into account the response of the patient and the dose concerned.

4.8 Undesirable effects
Undesirable effects are ranked by frequency, using the following convention:

Very common	(≥ 1/10)
Common	(≥ 1/100 to < 1/10)
Uncommon	(≥ 1/1 000 to < 1/100)
Rare	(≥ 1/10 000 to < 1/1 000)

Very rare (< 1/10 000)
Not known (cannot be estimated from the available data)

Metabolism and nutrition disorders
Common: decreased appetite

Psychiatric disorders
Common: irritability, aggression, restlessness, depression (in patients with a pre-existing depressive disorder, depressive moods may be aggravated), drug tolerance (especially during prolonged use), agitation.
Uncommon: abnormal behaviour, confusional state, anxiety, delusion, nightmares, loss of libido (reversible; occurs particularly with high doses or long-term treatment).
Frequency not known: dependence (particularly in cases of prolonged use; see section 4.4), initial insomnia, anger, hallucination, psychotic disorder, poor-quality sleep, suicidal ideation.

Nervous system disorders
Very common: somnolence (especially at the beginning of treatment and when higher doses are used).
Common: sedation, dizziness, impaired attention, slow speech/dysarthria/speech disorder (reversible; occurs particularly with high doses or long-term treatment), headache, tremor, ataxia.
Uncommon: emotional poverty, amnesia (may be associated with abnormal behaviour), memory impairment, anterograde amnesia (may occur in the normal dose range, but especially at higher dose levels).
Frequency not known: cognitive disorder, altered state of consciousness (particularly in elderly patients, may be combined with respiratory disorders), nystagmus (particularly with high doses or long-term treatment), gait disturbance (reversible; particularly with high doses or long-term treatment).

Eye disorders
Uncommon: diplopia (reversible; particularly with high doses or long-term treatment).

Respiratory, thoracic and mediastinal disorders
Frequency not known: respiratory depression, respiratory failure (may develop or worsen particularly in patients with pre-existing compromised respiratory function, e.g. in patients with asthma, or in patients with brain damage) (see sections 4.3 and 4.4).

Gastrointestinal disorders
Common: dry mouth, constipation, nausea.

Skin and subcutaneous tissue disorders
Uncommon: rash
Frequency not known: urticaria, Stevens-Johnson syndrome, toxic epidermal necrolysis (including some cases with fatal outcome).

Musculoskeletal and connective tissue disorders
Frequency not known: muscle spasms, muscle weakness.

General disorders
Very common: fatigue (especially at the beginning of treatment and when higher doses are used).
Frequency not known: slow response to stimuli, hypothermia.

Investigations
Uncommon: weight increased (particularly with high doses or long-term treatment).

Injury
Uncommon: risk of fall (risk of severe injuries) (see section 4.4).

4.9 Overdose

a) Symptoms of intoxication

Overdose and intoxication with Frisium and other benzodiazepines can cause depression of the central nervous system with the following symptoms: drowsiness, confusion and somnolence. The condition can progress to ataxia, respiratory depression, a drop in blood pressure and, in rare cases, coma. The symptoms of an overdose are more pronounced and may be life-threatening if other substances that affect the brain, including alcohol, are taken simultaneously.
Previous reports of overdose in the literature involving ingestion of up to ten times the recommended therapeutic daily dose did not result in any clinically significant damage. Symptoms included interruption of sleep by auditory stimuli or drowsiness and clouding of consciousness as well as weakness in the legs lasting a day.
Most cases of severe acute intoxication reported to the manufacturer involving Frisium have been of combined intoxication with other psychotropic drugs or hypnotics.
Three cases of overdose have been caused largely by Frisium itself. In two of these cases, the dose is unknown but serum levels of clobazam peaked at 2.8 and 1.5 mg/ml. In the third case, 880 mg was taken.
These three cases all resulted in a sleep-like or comatose state lasting 8 to 24 days. One patient did not react to pain stimuli for the first 5 days. In all cases, spontaneous breathing was unaffected.

b) Treatment of intoxication

In addition to monitoring respiration, pulse and blood pressure, gastric lavage, intravenous fluid replacement and general supportive measures are indicated.
Facilities for dealing with complications such as obstruction of the airways or respiratory failure must be available.
Hypotension can be treated with plasma replacement and, if necessary, sympathomimetics.
Secondary elimination (by means of forced diuresis or haemodialysis) is ineffective.
There is insufficient experience of additional administration of cholinergic physostigmine or the benzodiazepine antagonist flumazenil for an assessment of efficacy.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anxiolytic (tranquiliser) and anticonvulsant, 1, 5-benzodiazepine.

ATC-code: N05BA09.

Tranquilising effect

Experimental models with various animal species have shown clobazam to have a clearly pronounced tranquilising, anxiolytic and aggression-reducing effect. At therapeutically relevant doses, the tranquilising effect occurs without impairing motor activity.

Effect on motor coordination

Like all benzodiazepines, clobazam influences muscle coordination. However, it differs from other substances, e.g. diazepam and chlordiazepoxide, in that the impairment is much less severe.

Anticonvulsant effect

Various animal models have shown clobazam to have a pronounced anticonvulsant effect exceeding that of chlordiazepoxide.

Potentiation of anaesthesia and analgesic effect

Clobazam prolongs anaesthesia after administration of various barbiturates in mice. The narcotic effect of alcohol is also intensified by clobazam.

Clobazam was also found to have an analgesic effect in three different pain tests.

Cardiovascular effect

The effect of clobazam on the cardiovascular system has been tested in various animal species. A minimal effect, largely in the form of a slight decrease in blood pressure, pulse and respiratory rate, was only evident after a dose 20 to 200 times higher than the corresponding human dose.

5.2 Pharmacokinetic properties

Clobazam is virtually insoluble in water (1:12,500) and its apparent coefficient of distribution is 9 (n-octanol/phosphate buffer pH 7.4).

Absorption

After oral administration, clobazam is rapidly and extensively absorbed. Administration of clobazam as capsules, tablets or solution (in propylene glycol) has no significant effect on its relative bioavailability.

Time to peak plasma concentrations (t_{max}) is achieved after 0.5-4.0 hrs. The administration of clobazam tablets with food or crushed in apple purée slows the rate of absorption by approximately one hour but does not affect the overall extent of absorption. Clobazam can be given without regard to meals.

Concurrent alcohol consumption can increase bioavailability of clobazam by 50%.

Distribution

After a single dose of 20 mg of clobazam, marked interindividual variability in maximum plasma concentrations (222 to 709 ng/ml) was observed after 0.25 to 4 hours. Clobazam is lipophilic and distributes rapidly throughout the body. Based on a population pharmacokinetic analysis the apparent volume of distribution at steady-state was approximately 102 L, and is independent of concentration within the therapeutic range. Approximately 80-90% of clobazam is bound to plasma proteins, whereas binding to cellular blood components is minimal.

Following twice-daily administration, clobazam accumulates approximately 2-3 times the steady-state while the active metabolite N-desmethylclobazam (N-CLB) accumulates approximately 20 times. The steady-state concentration is reached within approximately 2 weeks.

Biotransformation

Clobazam is rapidly and extensively metabolised in the liver. Clobazam metabolism occurs primarily by hepatic demethylation to N-desmethylclobazam (N-CLB), mediated by CYP3A4 and to a lesser extent by CYP2C19. N-CLB is an active metabolite and the main metabolite found in human plasma.

N-CLB undergoes further biotransformation in the liver to form 4-hydroxy-N-desmethylclobazam, primarily mediated by CYP2C19.

CYP2C19 poor metabolisers exhibit a 5-fold higher plasma concentration of N-CLB compared to extensive metabolisers.

Clobazam is a weak CYP2D6 inhibitor. Co-administration with dextromethorphan leads to increases of 90% in AUC and 59% in C_{max} values for dextromethorphan.

Elimination

Based on a population pharmacokinetic analysis, plasma elimination half-lives of clobazam and N-CLB were estimated to be 36 hours and 79 hours, respectively.

Clobazam is cleared mainly by hepatic metabolism with subsequent renal elimination. In a mass balance study, approximately 80% of the administered dose was recovered in urine and about 11% in the faeces. Less than 1% of unchanged clobazam and less than 10% of unchanged N-CLB is excreted through the kidneys.

Clobazam crosses the placental barrier and can also be detected in breast milk. Active clobazam concentrations can be reached in fetal blood and breast milk.

5.3 Preclinical safety data

Repeated dose toxicity

Repeated dose toxicity studies in rats showed a dose-dependent reduction in spontaneous activity after an oral daily dose of 12-1 000 mg of clobazam per kg. A decrease in weight gain, respiratory depression and hypothermia were seen at the highest dose.

Studies in dogs initially showed dose-dependent sedation, somnolence, ataxia and slight tremor after a daily dose of 2.5-80 mg/kg. Later, these symptoms almost completely

disappeared. Similar dose-dependent effects were observed in monkeys after an oral daily dose of 2.5-20 mg/kg of clobazam.

Reproductive toxicity
Clobazam did not impair fertility in mice at doses of 200 mg/kg daily and in rats at doses of 85 mg/kg daily. Also, in another fertility study, the fertility of male and female rats was not impaired up to the maximum oral dose of 750 mg/kg/day.

In studies concerning embryo-fetal development, an increase of fetal mortality and developmental delay of the fetus with respect to skeletal variations was observed in rats at oral doses of 150-750 mg/kg/day.

In rabbits, oral doses over 30 mg/kg/day resulted in decreased fetal body weights and increased visceral and skeletal malformations of the fetus. Oral administration of the highest dose of 75 mg/kg/day additionally resulted in increased fetal mortality, presumably due to maternal toxicity.

In a study concerning pre- and postnatal development in rats, pup survival was decreased at oral doses over 350 mg/kg/day. Additionally, the young animals showed increased motor activity at all doses ($\geq$ 50 mg/kg/day).

In all these studies, the plasma exposures of rats and rabbits for clobazam and N-desmethylclobazam (AUC) were lower than those of humans at the maximum recommended human dose of 80 mg/kg/day.

Carcinogenic and mutagenic potential
A significant increase in the incidence of follicular cell adenoma was found in rats in the highest dose group (100 mg/kg of body weight). It is known that clobazam, like other benzodiazepines, leads to activation of the thyroid in rats. These changes have not been observed in studies of other species (mice, dogs and monkeys). Clobazam is not genotoxic and does not transform cells. No effects on thyroid function have been observed in humans at the clinically relevant dose range (20-80 mg).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Excipients: Lactose, maize starch, colloidal anhydrous silica, talc, magnesium stearate.

6.2 Incompatibilities
Not applicable

6.3 Shelf life
Do not use later than the date of expiry

6.4 Special precautions for storage:

Keep medicines out of the reach of children
Do not store above 30ºC

6.5 Nature and contents of container

10, 20 and 100 tablets. Not all pack size maybe marketed.
Hospital packs

6.6 Special precautions for disposal and other handling

No special requirements.

7. Holder/ Distributor

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

Manufacturer

Opella Healthcare International SAS
56, route de Choisy au Bac
60205 Compiĕgn, France

8. Date of last revision

Apr 2022
(CCDS V6, 7, 8.1)

Please note the following information for the patient:
This preparation contains a "benzodiazepine".
Benzodiazepines are drugs for the treatment of certain diseases which are associated with restlessness and anxiety states, inner tension or insomnia. When using benzodiazepines, there is a risk of developing or promoting dependence, to minimize this risk, you are advised to observe the following instructions exactly:

1. Benzodiazepines have been developed solely for the treatment of a specific group of illnesses, and may only be taken on doctor's instructions.

2. When these drugs have been taken for a maximum of four weeks, the doctor should decide whether the treatment is to be continued. An uninterrupted, prolonged period of administration should be avoided, as it may lead to dependence. If these drugs are taken without consulting the doctor, the chance of them helping you is reduced.

3. On no account increase the dose prescribed by the doctor, even if the effect has lessened. Treatment will not have the desired effect if you increase the dose on your own initiative.

4. When benzodiazepines are discontinued after prolonged use, restlessness, anxiety states, and insomnia may occur, often after a delay of several days. These withdrawal symptoms usually disappear after 2-3 weeks.

5. Tell your doctor if you have suffered or are still suffering from alcohol, or drug dependence, or hard drug addiction. If this is the case, you must not take benzodiazepines, except in rare situations determined only by the doctor.

6. Never take benzodiazepine-containing drugs because “they have been such a help to someone else”, and do not pass the preparations on to others.